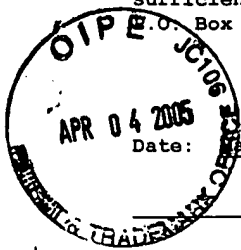


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Dennis P. Tramaloni

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PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Group No.: 1631

Ulrich Certa, et al.

Serial No.: 10/802,432

Filed: March 17, 2004

For: GENE TRANSCRIPTION ASSAY METHOD

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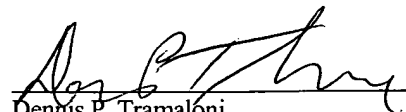
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Dear Sir:

Attached please find the certified copy of the foreign application from which priority is claimed for this case:

<u>Country</u>	<u>Application No.</u>	<u>Filing Date</u>
Europe	03006263.2	March 21, 2003

Respectfully submitted,



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Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

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Patentanmeldung Nr. Patent application No. Demande de brevet n°

03006263.2

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Anmeldung Nr:
Application no.: 03006263.2
Demande no:

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Date of filing: 21.03.03
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Anmelder/Applicant(s)/Demandeur(s):

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SUISSE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
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Transcriptional activity assay

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s)
revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

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69
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Case 21574

Transcriptional Activity Assay

Field of the invention

5 The present invention relates to a novel method for determining the biological activity of compounds which can modulate gene transcription, and based on this method, a method for the determination of the relative biological activity of a compound and a method for the identification of compounds which modulate gene transcription. The methods of this invention are particularly useful for identifying compounds that may be of
10 use in the treatment of diseases which depend on the modulation of gene transcription within affected cells and tissues.

Background

15 The biological activity of compounds that regulate cellular functions such as cell proliferation or viral protection is commonly determined by measuring increases or decreases of binding activities of these factors and/or compounds either to native or recombinant receptors in vitro, or in cell-based binding assays. A disadvantage of these assays for the evaluation of the biological activity of compounds resides in the fact that the
20 binding affinity does not necessarily correlate with the biological activity of a compound.

A more direct and, therefore, more reliable determination of the biological activity of compounds can be achieved by well known assays such as cell proliferation, cell survival or cell migration assays. Such assays are, however, more cumbersome, especially for larger scale screenings. In many cases, compounds which regulate such cellular activities also
5 modulate gene transcription. Thus, the biological activity of such compounds may be determined by measuring the modulation of gene transcription, which is commonly done by reporter assays, which necessitate the generation of recombinant cells expressing a suitable reporter construct. Alternatively, the biological activity of such compounds may be determined by measuring the expression of suitable target genes, eg. by Northern Blot
10 analysis or quantitative PCR, which is, however not efficient.

Description of the invention

15 The problem of the present invention was to provide a reliable and easy method for the determination of the biological activity of a modulator of transcriptional activity which lacks the disadvantages of binding assays, but is more efficient than the commonly used activity assays.

20 Surprisingly, it was found that the biological activity of a compound can be determined more reliably by using a novel method based on the determination of the general transcriptional gene response induced by said compound comprising quantitation of signal intensities of genes which are transcriptionally regulated by said compound.

25 The present invention provides a novel method for determining the biological activity of a compound which can modulate gene transcription, comprising the steps of a) contacting a host with a compound; b) determining the general transcriptional gene response of the host; and c) quantitating the general transcriptional gene response induced by said compound. Preferably, the biological activity of said compound is given by the sum
30 of the normalised average difference of signal intensities quantitated in step c). In a more preferred embodiment of the present invention the general transcriptional gene response

is determined by an DNA array technology. In an even more preferred embodiment, the array technology is an oligonucleotide array technology. Preferably the DNA or oligonucleotide arrays are high density DNA or oligonucleotide arrays. Such arrays, and methods of analysing DNA or RNA using such arrays have been described previously, eg. in EP0834575, EP0834576, WO96/31622, US5837832 or WO98/30883. WO97/10365 provides methods for monitoring of expression levels of a multiplicity of genes using high density oligonucleotide arrays. In a most preferred embodiment, the oligonucleotide arrays are GeneChip arrays.

10 The term " general transcriptional gene response " as used herein refers to the biological activity of a compound given by the sum of the normalised average difference of signal intensities of genes regulated by said compound in a responsive host. The determination of the general transcriptional gene response is achieved by hybridizing labeled cDNA from the treated hosts with DNA or more preferably oligonucleotide arrays.

15 The raw data of the arrays is then measured, eg. with a confocal laser scanner (Hewlett Packard, U.S.) as a non-limiting example, and pixel levels are analysed using commonly known methods. The expression level for each gene is calculated as a normalised average difference of intensity as compared to hybridisation to mismatched oligonucleotides, and expressed in arbitrary units (AD). Four criteria are applied to select differentially expressed

20 genes: (1) The intensity value of treated cells was at least two fold higher than the intensity value of untreated cells. (2) The intensity value in the treated cells should be higher or at least 50 arbitrary units (AD). (3) The intensity value of the untreated cells should be lower than 50 AD. (4) The standard deviation has to be significantly lower than the absolute change in average difference and the calculated confidence level of a gene is set to greater

25 than 97% (p value < 0.03). The general transcriptional gene response of the host induced by a compound is then quantitated by obtaining the sum of the normalised average difference of signal intensities (sum of arbitrary units, Σ AD).

30 The non-limiting examples described hereinafter demonstrate that the results obtained with this novel method more reliably correlate with biological activity than do binding assays, with the additional advantage of being efficient. They also show that it determining the general transcriptional gene response by the method of the present invention is more reliable than the determination of the transcriptional expression levels of an individual gene or a small selection of genes.

The host used for the method of the present invention may be a whole non-human organism, which includes, but is not limited to a transgenic or a knockout animal; specific types of tissue from any species, which includes, but is not limited to, liver, heart, kidney, or primary cell isolates, such as blood cells or primary cells isolated from a tissue, or cell lines. The host or hosts used to determine the biological activity of a compound by the present invention has to be responsive to a compound of interest. The term "responsive" as used herein refers to the ability of a host to exhibit elevated or reduced transcription of genes in response to a compound. As a non-limiting example, a melanoma cell line ME15 (CNCM I-2546 in WO02/18633) can be used to determine the biological activity of PEG-IFN or PEG-IFN isoforms by the method of the present invention.

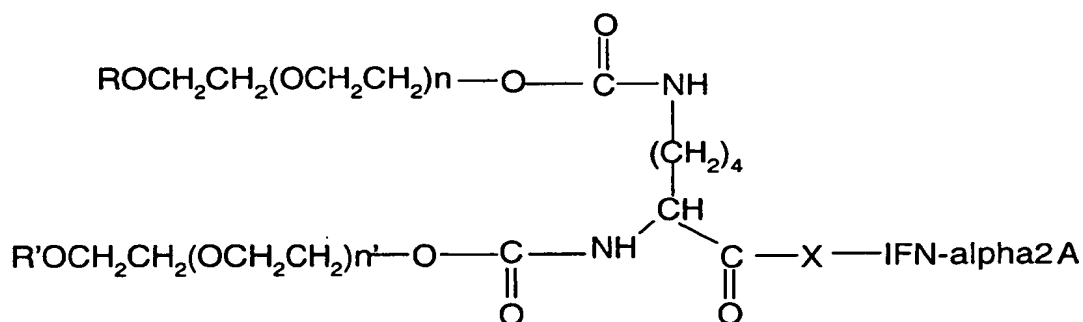
The major advantages of the present invention, as compared to the commonly used activity assays or methods for determining gene transcription such as reporter assays or Northern Blotting are that the method does not require the preparation of any cell lines transfected with reporter constructs, and it allows for an easy and efficient analysis of a multitude of genes that are transcriptionally regulated, thus rendering the activity assays more efficient and reliable. Furthermore, as shown in Figure 4, binding activities do not always correlate with biological activity, while the determination of the transcriptional activity of compounds based on the determination of the general transcriptional gene response does correlate. Thus, the method of the present invention allows a more accurate determination of the biological activity of compounds than do binding assays.

In one embodiment, the compound of the method hereinbefore described is a modified compound, more preferably a modified protein, even more preferably a pegylated protein, or most preferably, a specific isolated isoform of a pegylated protein. Preferably, the pegylated protein is erythropoietin (EPO) or interferon (IFN).

The term "PEG-IFN" as used herein includes IFN- α s derived from any natural material (e.g., leukocytes, fibroblasts, lymphocytes) or material derived therefrom (e.g. cell lines), or those prepared with recombinant DNA technology. Details of the cloning of IFN α and the direct expression thereof, especially in *E. coli*, have been the subject of many

publications. The preparation of recombinant IFN α s is known, for example from Goeddel et al. (1980) *Nature* 284, 316-320 and (1981), *Nature* 290, 20-26, and European Patents Nos. 32134, 43980 and 211148. There are many types of IFN α such as IFN α I, IFN α 2; and further their subtypes including but not limited to IFN α 2A, IFN α 2B, IFN α 2C and IFN α II (also designated IFN α II or ω -IFN). The term "IFN α " also includes consensus IFN α available from Amgen or mixtures of natural and/or recombinant IFN α s. The use of IFN α 2A is preferred. The manufacture of IFN α 2A is described in European Patents Nos. 43980 and 211148.

The IFN- α is conjugated to a polymer such as a polyalkylene glycol (substituted or unsubstituted), for example, polyethylene glycol, to form PEG-IFN- α conjugate. Conjugation may be accomplished by means of various linkers known in the art, in particular by linkers such as those disclosed in European Patent Applications, Publication Nos. 0510356, 0593868 and 0809996. The molecular weight of the polymer, which is preferably polyethylene glycol, may range from 300 to 70,000 daltons, and one or more, preferably one to three, polymers may be conjugated to the IFN- α . A preferred PEG-IFN- α conjugate has the formula:



where R and R' are methyl, X is NH, and n and n' are individually or both either 420 or 520.

In another preferred embodiment of the method hereinbefore described, the transcriptionally regulated genes are one or more genes selected from the group consisting of Seq ID No. 1 to 29, which are also listed in Table 1.

The method of the present invention is suitable for the analysis of any compound that modulates gene transcription in any type of host. Modulation of gene transcription includes both upregulation or downregulation of gene transcription.

5 The method hereinbefore described is the basis for a method for determining the relative biological activity of a modified compound, comprising measuring the biological activity of the modified compound and the respective unmodified compound by the method hereinbefore described, wherein the relative transcriptional activity of the modified protein is determined by calculating the ratio of the biological activity of the modified compound and the biological activity of the unmodified compound. Preferably, 10 the modified compound is a chemically or enzymatically modified compound. More preferably, the modified compound is a pegylated protein. Thus, this method provides an easy assay to compare the biological activity of modified compounds with their unmodified counterparts. In a preferred embodiment, the present invention allows to 15 select the isoform of a compound with the highest biological activity isolated from a mixture of isoforms, most preferably from pegylated proteins.

The compounds whose biological activity can be determined by the method of this invention include any compound that can modulate gene transcription. These compounds 20 can be proteins, polypeptides, nucleic acids, polymers or small molecules. Many proteins, polypeptides, nucleic acids, polymers or small molecules can modulate gene transcription, either directly, by acting as transcription factors, or indirectly, by inducing signalling cascades that ultimately up- or downregulate gene transcription or alternatively, by interfering with other compounds that modulate gene transcription. The following list of 25 compounds whose biological activity can be determined by the method of the present invention exemplifies in a non-limiting way the kinds of compounds, including proteins and polypeptides, for which the method of the present invention can be used.

Among these non-limiting examples are hormones, such as retinoid acid, that induce 30 nuclear hormone receptors, which are transcription factors (A. Rowe: Retinoid X receptors, *Int. J. Biochem. Cell Biol.*, 29 (1997), 275-278; and CK. Glass: Some new twists in the regulation of gene expression by thyroid hormone and retinoic acid receptors, *J. Endocrinol.*, 150 (1996), 349-357). The method of the present invention may be used to

determine the biological activity of such hormones and their nuclear hormone receptors, and it may also be used to identify compounds that interfere with the transcriptional activity of such nuclear hormone receptors. Thus, the present invention may, for example, be useful for identifying and analysing inhibitors of nuclear hormone receptors such as RXR or LXR.

Further to hormones that activate nuclear hormone receptors, the method of this invention may also be used to determine the biological activity of other hormones which activate signalling cascades that lead up to the modulation of gene transcription. As a non-limiting example, such hormones include erythropoietin (Epo), which is known to modulate gene transcription (Z.Z.Chong et al: Hematopoietic factor erythropoietin foster neuroprotection through novel signal transduction cascades, *J. Cereb. Blood Flow Metab.*, 22 (2002), 503-514; D.M. Wojchowski and T.C. He: Signal transduction in the erythropoietin receptor system, *Stem. Cells*, 11 (1993), 381-392; J.L. Spivak: The mechanism of action of erythropoietin, *Int. J. Cell Cloning*, 4 (1986), 139-166; and L. Mulcahy: The erythropoietin receptor, *Semin. Oncol.* 28 (2001), 19-23).

Cytokines and growth factors are known to induce signalling cascades that lead to a modulation of gene transcription. Thus, as a non-limiting example, the method of the present invention may also be used to identify agonists or antagonists of cytokines and growth factors, and to determine their biological activity. Such cytokines and growth factors include, but are not limited to, Interferons, Tumor Necrosis Factor, Vascular Endothelial Growth Factor (T. Hanada and A. Yoshimura: Regulation of cytokine signaling and inflammation, *Cytokine Growth Factor Rev.*, 13 (2002), 413-421; and Y. Sato et al.: Properties of two VEGF receptors, Flt-1 and KDR, in signal transduction, *Ann. N Y. Acad. Sci.*, 902 (2000), 201-207).

Further to this, the method of the present invention may be used to determine the biological activity of modified or mutated proteins or polypeptides. Modification may be achieved either chemically or enzymatically. A non-limiting example for this application is the determination of the biological activity of different isoforms of pegylated Interferon, which is shown in the Figures attached to this application. Thus, the present invention provides for determining the relative biological activity of a modified compound,

comprising measuring the biological activity of the modified compound and the respective unmodified compound by the method hereinbefore described, wherein the relative transcriptional activity of the modified protein is determined by calculating the ratio of the biological activity of the modified compound and the biological activity of the unmodified compound. Preferably, the modified compound is a chemically or enzymatically modified compound. Most preferably, the modified compound is a pegylated protein.

The method of the present invention may also be used for identifying and characterizing modulators of enzymes which, as a downstream event, can cause a modulation of gene transcription. A non-limiting example for such enzymes are phosphodiesterases (PDE), preferably PDE4, most preferably PDE4D isoenzymes. The PDE4D isoenzymes are preferably selected from the group consisting of PDE4D1, PDE4D2, PDE4D3, PDE4D4, PDE4D5, PDE4D6, PDE4D7 and PDE4D8. PDEs degrade cyclic AMP, a second messenger which can modulate gene transcription (G.S. McKnight: Cyclic AMP second messenger systems, *Curr. Opin. Cell Biol.*, 3 (1991) 213-7), and potent PDE inhibitors were found to modulate gene transcription (B. Wagner et al.: 7-Benzylamino-6chloro-2piperazino-4-pyrrolidino-pteridine, a potent inhibitor of cAMP-specific phosphodiesterase, enhancing nuclear protein binding to the CRE consensus sequence in human tumour cells, *Biochemical Pharmacology*, 63 (2002) 659-668; Y. Nishio et al.: Cilostazol, a cAMP phosphodiesterase inhibitor, attenuates the production of monocyte chemoattractant protein-1 in response to tumor necrosis factor-alpha in vascular endothelial cells, *Hormone & Metabolic Research*, 29 (1997) 491-495). Thus, the method of the present invention may be used for screening of modulators of such enzymes.

25

Among the compounds that can be identified and analysed are also functional antibodies. Functional antibodies are antibodies that either inhibit or stimulate the function(s) of the protein that they bind to. This type of antibodies has been raised against numerous target proteins, and some of these antibodies are also of therapeutic value. Amongst these are, as a non-limiting example, anti-Her2/ErbB2 antibodies, also called Herceptin antibodies. These antibodies are being successfully used in the treatment of breast cancer. They function by inhibiting the activation of human epidermal growth factor receptor Her2/ErbB2, which plays a pivotal role in many types of cancer, including breast cancer. Like many other growth factor receptors, Her2, when bound by its ligand(s),

30

mediates signalling including modulation of gene transcription. It has been shown that Herceptin is capable of modulating gene transcription in cells that express Her2/ErbB2 (A.H. Talukder et al.: Antihuman epidermal growth factor receptor 2 antibody herceptin inhibits autocrine motility factor (AMF) expression and potentiates antitumor effects of AMF inhibitors, *Clin. Cancer Res.* 8 (2002), 3285-3289; and R. Mandler et al.: Modification in synthesis strategy improve the yield and efficacy of geldanamycin-herceptin immunoconjugates, *Bioconjugate Chemistry*, 13 (2002), 786-791). Currently, eight different Herceptin antibodies exist, and more may still be produced. Generally, in the case of functional antibodies, the method of the present invention may be used in determining which antibody displays the highest biological activity and would be the most suited for therapeutic use. Thus, the method of the present invention is also suitable for determining the biological activity of antibodies, eg. for the identification of inhibitory or stimulating antibodies. In a preferred embodiment, the antibody is an antibody of therapeutic value. In a more preferred embodiment, the antibody is a Herceptin antibody.

15

For the identification and analysis of a compound that acts indirectly by inhibiting or stimulating the biological activity of a second compound, such as a hormone, cytokine, growth factor, enzyme etc., the present invention provides a method for identifying compounds that indirectly modulate gene transcription comprising determining the biological activity of a first compound which is a known modulator of gene transcription by the methods hereinbefore described in the presence or absence of a second compound, wherein a compound which indirectly modulates gene transcription is identified if the biological activity of the first compound measured in the presence of said second compound is significantly different from the biological activity of the first compound measured in the absence of said second compound.

25

The present invention provides a compound identified by the methods hereinbefore described which modulates gene transcription. A use of the methods hereinbefore described for identifying a compound which modulates gene transcription is provided as well. The present invention also provides a kit comprising components for carrying out the methods hereinbefore described. Preferably, said components comprise a DNA array, more preferably an oligonucleotide array.

30

Furthermore, a pharmaceutical composition comprising a compound identified by the methods hereinbefore described and a pharmaceutically acceptable carrier is provided. Any conventional carrier material can be utilized. The carrier material can be an organic or inorganic one suitable for eteral, percutaneous or parenteral administration. Suitable
5 carriers include water, gelatin, gum arabic, lactose, starch, magnesium stearate, talc, vegetable oils, polyalkylene-glycols, petroleum jelly and the like. Furthermore, the pharmaceutical preparations may contain other pharmaceutically active agents. Additional additives such as flavoring agents, stabilizers, emulsifying agents, buffers and the like may be added in accordance with accepted practices of pharmaceutical compounding.

10

Additionally, the present invention provides a method for the production of a pharmaceutical composition comprising the steps of identifying a compound by the method of the present invention, modifying the identified compound and formulating the compound obtained with a pharmaceutically acceptable carrier or diluent.

15

The present invention also provides a use of a compound identified by the methods hereinbefore described or a pharmaceutically acceptable salt thereof for the preparation of a medicament for the treatment of a disease, preferably of a viral disease or of a cancer.

20

The term "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

25

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the identified agents wherein the parent agent is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues
30 such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such

conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, benzenesulfonic, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

Also claimed are the methods, compounds, kits and uses as hereinbefore described, especially with reference to the foregoing examples.

10

Having now generally described this invention, the same will become better understood by reference to the specific examples, which are included herein for purpose of illustration only and are not intended to be limiting unless otherwise specified, in connection with the following figures.

15

Brief description of the figures:

Figure 1:

20 Analytical IEC-HPLC of 180µg of PEG-IFN. An analytical strong-cation exchange column was used to separate the positional isomers (TOSOH-BIOSEP, SP-5PW, 10 µm particle size, 7.5 mm diameter and 7.5 cm length).

Figure 2:

25 (A) Specific antiviral activity of the 9 positional isomers and PEG-IFN

The figure shows the specific antiviral activity [U/µg] of the positional isomers. The antiviral activity was determined in MDBK cells infected with vesicular stomatitis virus.

(B) Specific antiproliferative activity of the isomers and PEG-IFN

This figure indicates the specific inhibition of proliferation [OD_{490nm}/μg] on the ME15 cells with 100 U/ml of the each positional isomer and PEG-IFN.

The results present the averages of three assays performed independently. The specific antiviral activity and specific antiproliferative activity of PEG-IFN is given for comparison (hatched line).

Figure 3:

Time dependent inhibition of proliferation in a melanoma cell line (ME-15) The ME15 cell line was cultured in presence of different concentrations (500,125, and 15 U/ml) IFN, PEG-IFN and isomers over 5 days. The cell proliferation was measured every 24h. The control cell density after 5 days was set as 100% as references. The data are derived from three independent culture replicates.

Figure 4:

Correlation of the kinetic dissociation constant and specific antiviral activity of the PEG-IFN and isomers with high (K134), intermediate (K131, K164) and low (K121) specific antiviral activity.

Figure 5:

- (A) Correlation of specific antiviral activity, specific antiproliferative activity and specific transcriptional response of each isomer. The PEG-IFN was set as 100% value reference. The hatched line indicates the biological and transcriptional activity of PEG-IFN. The sum Σ relative mRNA abundance (AD) is illustrated as the sum of all inducible genes for each isomer.
- (B) Hierarchical clustering of AD of the different general transcriptional gene response from 100 U/ml IFN, PEG-IFN and the isomers. The incubation time of the IFN and the pegylated variants was 48h; the cell line used is an IFN-sensitive melanoma cell line (ME15). The conditions for the data analysis are described in the text. The data of the different expression profiles of the genes are reported in Table 2.

Figure 6:

3D-Structure based Model for PEG-IFN mediated interferon responses. Arrangement of the positional PEG-IFN isomers in 4 groups according to the specific antiviral and antiproliferation activity. The high resolution structure of human interferon alpha-2a was determined with NMR spectroscopy (Klaus et al.: The three-dimensional high resolution structure of human interferon alpha-2a determined by heteronuclear NMR spectroscopy in solution. *J. Mol. Biol.* 274 (1997); 661-675). The pegylation sites of interferon alpha-2a are colored red.

10

Examples

Antiviral and antiproliferative roles of IFN

15 Interferon alpha-2a (IFN) plays an important role in mediating antiviral and antiproliferative responses and in modulating immune responses (G.R. Stark: How cells respond to interferons, *Annu. Rev. Biochem.* 67 (1998), 227-264). These biological activities make IFN important as an inhibitor of disease pathogenesis and useful in the treatment of viral infection and some cancers (S. Zeuzem, et al. : Peginterferon alfa-2a in patients with chronic hepatitis C, *New England Journal of Medicine* 343 (2000), 1666-1172). Since 1986 recombinant human IFN (ROFERON-A) has become an important therapeutic agent to treat patients with viral and oncological diseases (S. Zeuzem et al.: Peginterferon alfa-2a (40 kDa) monotherapy: a novel agent for chronic hepatitis C therapy, *Expert Opinion on Investigational Drugs* 10 (2001), 2201-2213).

25

The success of IFN treatment in the clinic is partly limited due to its short serum half-life (4 - 6h). Peak concentrations of IFN occur 3-8 h following iv. or sc. administration and large fluctuations in serum concentrations can occur after each dose. After 24 h, the amount of exogenous IFN remaining in the body is negligible such that the thrice-weekly regimen used is unlikely to maintain concentrations required for antiviral

30

activity (J.M. Harris et al.: Pegylation: A novel process for modifying pharmacokinetics, *Clin. Pharmacokinet.* 40 (2001), 539-551; P. Bailon et al.: Rational design of a potent, long-lasting form of interferon: A 40 kDa branched polyethylene glycol-conjugated Interferon-2a for the treatment of hepatitis C *Bioconjugate Chem.* 12 (2001), 195-202).

5

Administration frequency of IFN is dependent on the disease. For example, the standard therapeutic application of IFN consists of 3 million international units administered subcutaneously three times per week for up to 48 weeks (J.M. Harris et al.: Pegylation: A novel process for modifying pharmacokinetics, *Clin. Pharmacokinet.* 40 (2001), 539-551), while certain oncological indications may require daily administration (P. Bailon et al.: Rational design of a potent, long-lasting form of interferon: A 40 kDa branched polyethylene glycol-conjugated Interferon-2a for the treatment of hepatitis C, *Bioconjugate Chem.* 12 (2001), 195-202). In order to improve the pharmacokinetic and pharmacodynamic properties of IFN, it was conjugated with poly(ethylene glycol) (PEG).

15

Since several years, studies have been carried out to assess the influence of the various PEG sizes and PEG types on in vitro and in vivo bioactivity. These results showed the important correlation of the PEG characteristics and the biological activity. For example, branched PEG moieties may more effectively cloak and protect IFN from proteolytic degradation than the linear PEG attachments and may also enhance the absorption and distribution properties of protein. Another effect is that increasing the molecular weight of the PEG moiety, decreases the clearance of the therapeutic molecule, thereby producing sustained exposure to the virus (J.M. Harris et al.: Pegylation: A novel process for modifying pharmacokinetics, *Clin. Pharmacokinet.* 40 (2001), 539-551). Based on this knowledge coupled with the latest advancements in pegylation procedures, a long-lasting, branched monopegylated IFN was developed (P. Bailon et al.: Rational design of a potent, long-lasting form of interferon: A 40 kDa branched polyethylene glycol-conjugated Interferon-2a for the treatment of hepatitis C, *Bioconjugate Chem.* 12 (2001), 195-202).

30

An interferon alpha-2a conjugated via an amide linkage with a branched 40kDa PEG (PEG-IFN), exhibits sustained adsorption and reduced renal clearance, resulting in strong antiviral pressure throughout a once-weekly dosing schedule (M.C. Perry and B. Jarvis: Peginterferon- α -2a (40 kD): A review of its use in the management of chronic hepatitis C,

Drugs 15 (2001), 2263-2288; and M.W. Lamb and E.N. Martin: Weight-Based versus fixed dosing of peginterferon (40 kDa) alfa-2a, *The Annals of Pharmacotherapy* 36 (2002), 933-938). The characterization of this PEG-IFN mixture indicated 9 positional isomers which are monopegylated on lysines: K₃₁, K₄₉, K₇₀, K₈₀, K₁₁₂, K₁₂₁, K₁₃₁, K₁₃₄ and K₁₆₄. All
5 positional isomers induced viral protection of MDBK cells in the Anti-Viral Assay.

Example 1: Preparation of PEG-IFN

The PEG-IFN was manufactured by Hoffmann-La Roche Inc. The pegylated
10 interferon alpha-2a was prepared by the conjugation of lysine ϵ -amino groups at the surface of the interferon molecule with an activated branched polyethylene glycol derivative of molecular weight 40000 Da (Bailon, P. et al.: Rational design of a potent, long-lasting form of interferon: A 40 kDa branched polyethylene glycol-conjugated Interferon-2a for the treatment of hepatitis C. *Bioconjugate Chem.* 12 (2001); 195-202;
15 EP809996). The isolation and characterization of the isomers of PEG-IFN is described below. All other reagents and chemicals were of the highest purity available.

PEG-IFN consists of a mixture of monopegylated IFN molecules. In each molecule one single lysine is chemically modified by the attachment of a PEG moiety resulting in a
20 mixture of several species. Due to the presence of eleven lysines and a free N-terminal amino group twelve monopegylated species are expected, but only nine lysine-modified species could be found (K₃₁, K₄₉, K₇₀, K₈₃, K₁₁₂, K₁₂₁, K₁₃₁, K₁₃₄ and K₁₆₄).

Example 2: Purification and characterization of positional PEG-IFN isomers

25

We developed a preparative two step chromatography method allowing efficient separation of these species. The purity of the prepared positional isomers could be checked by an analytical ion exchange method, see an example for an elution profile in Figure 1. Separation is based on local charge differences of the isomers resulting from the different
30 pegylation sites on the protein moiety. The decrease of the baseline absorption towards the

end of the chromatogram suggests that there were no other monopegylated species of IFN eluting at higher retention time. By two step separation nine positional isomers were purified, the characterization of the isomers indicate the pegylation sites are all on lysines: K31, K49, K70, K83, K112, K121, K131, K134 and K164.

5

Example 3: Separation of the positional isomers

A two-step isolation and purification scheme was used to prepare the monopegylated isoforms of PEG-interferon alpha 2a.

10

a) The first step was a separation of the positional isomers on a preparative low pressure liquid chromatography column with a weak-cation exchange matrix (TOSOH-BIOSEP, Toyopearl CM-650S, Resin Batch no. 82A having a ion exchange capacity of 123 mEq/ml, the diameter of the column being 16 mm, the length 120 cm). A linear pH-
15 gradient of increasing sodium acetate concentration (25 mM, pH 4.0 up 75 mM to pH 7.8) was applied at a flow rate of 0.7 mL/min. Detection was at 280 nm. With this chromatographic step species 1, 2, 5, 6 and a mixture of 3, 4, 4a, 7 and 8 could be collected, see Table 1.

20

b) The fractions were further separated and purified in the second preparation step. A preparative column with the same matrix as the analytical strong-cation exchange column as described above but larger dimensions (30 mm i.d. and 70 mm length), further a higher flow rate and an extended run time was used. As for the analytical method the column was pre-equilibrated with 3.4 mM sodium acetate, 10% ethanol and 1% diethylene
25 glycol, adjusted to pH 4.4 (buffer A). After loading the PEG-IFN samples, the column was washed with buffer A, followed by an ascending linear gradient to 10 mM dibasic potassium phosphate, 10% ethanol and 1% diethylene glycol, adjusted to pH 6.6 (buffer B). The flow rate was 1.0 mL/min and the detection at 218 nm.

30

The protein concentration of the PEG-IFN alpha 2a isomer was determined by spectrophotometry, based on the 280 nm absorption of the protein moiety of the PEG-IFN alpha 2a.

An analytical elution profile of 180 µg of PEG-IFN alpha 2a is shown in Fig.1. The result of this method is a separation into 8 peaks, 2 peaks with baseline separation and 6 with partial separation. The decrease of the baseline absorption towards the end of the chromatogram suggests that there were no other monopegylated species of IFN alpha 2a eluting at higher retention time.

In addition, looking carefully at the IEC-chromatogram a further peak close to the detection limit is visible between peaks 2 and 3 indicating the presence of additional positional isomers that should also contribute to the specific activity of the PEG-IFN alpha 2a mixture. Additional species were expected as the interferon alpha-2a molecule exhibits 12 sites for pegylation (11 lysines and the N-terminus). However, given the low abundance of these species, they were not isolated and characterised.

Isomer samples derived from IEC optimisation runs were investigated directly after the isolation ($t = 0$) and after 2 weeks of storage at 5°C. No significant differences were observed for the protein derived from IEC-peaks with regard to the protein content as determined by spectrometric methods; nor were any changes to be detected in the monopegylation site, the content of oligo-PEG-IFN alpha 2a, the amount of aggregates and the bioassay activity. Taking into account the relative abundance of the individual isomers - as determined by the IEC method - as well as the specific activities - as determined in the anti-viral assay - almost the total specific bioactivity of the PEG-IFN alpha 2a mixture used for their isolation is recovered (approximately 93%).

The analytical IE-HPLC was used to check the purity of the individual isomers with respect to contamination with other positional isomers in the IEC fractions. The peaks 2, 3, 4, 4a, 5 and 7 had more than 98%, the peaks 1 and 8 had 93% and peak 6 had 88 % purity.

Table 1:

PEG-peptides identified by comparison of the Lys-C digest spectra of the isomers and the reference standard.

Identified PEG Sites in the separated PEG-IFN Species

Peak		missing peaks in peptide map	
PEG-IFN	PEG site	M _r (DA)	Sequence
Peak 1	K ³¹	A, E	24-49
Peak 2	K ¹³⁴	I, I'	134-164
Peak 3	K ¹³¹	C	122-131 ^a
Peak 4	K ¹²¹	B, C	113-131
Peak 4a	K ¹⁶⁴	b	134-164 ^{a,b}
Peak 5	K ⁷⁰	D, F	50-83
Peak 6	K ⁸³	D, H	71-112
Peak 7	K ⁴⁹	E, F	32-70
Peak 8	K ¹¹²	B, H	84-121

^a 132-133 too small to detect.

5 ^{a,b} RP-HPLC.

The fractions were characterised by the methods described herein.

Example 4: Analysis of the fractions by mass spectrometry peptide mapping

10 Mass spectra were recorded on a MALDI-TOF MS instrument (PerSeptive Biosystems Voyager-DE STR with delayed extraction). Each IEC fraction (Ion Exchange Chromatography) was desalted by dialysis, reduced with 0.02 M 1,4-dithio-DL-threitol (DTT) and alkylated with 0.2 M 4-vinyl pyridine. Then the proteins were digested with
 15 endoproteinase Lys-C (Wako Biochemicals) in 0.25 M Tris (tris(hydroxymethyl)-aminoethane) at pH 8.5 with an approximate enzyme to protein ratio of 1:30. The reaction was carried out over night at 37 °C.

A solution of 20 mg/ml α -cyano-4-hydroxycinnamic acid and 12 mg/ml nitrocellulose in acetone/isopropanol 40/60 (v/v) was used as matrix (thick-layer application). First, 0.5 μ L of matrix was placed on the target and allowed to dry. Then, 1.0 μ L of sample was added. The spectra were obtained in linear positive ionisation mode with an accelerating voltage of 20.000 V and a grid voltage of 95 %. At least 190 laser shots covering the complete spot were accumulated for each spectrum. Des-Arg¹-bradykinin and bovine insulin were used for internal calibration.

Example 5: High-performance liquid chromatography (RP-HPLC) Peptide Mapping

10

The peptides were characterized by reverse-phase high-performance liquid chromatography (RP-HPLC) Peptide Mapping. The IEC fractions were reduced, alkylated and digested with endoproteinase Lys-C as described for the MALDI-TOF MS peptide mapping. The analysis of the digested isomers was carried out on a Waters Alliance HPLC system with a Vydac RP-C18 analytical column (5 μ m, 2.1 \times 250 mm) and a precolumn with the same packing material. Elution was performed with an acetonitrile gradient from 1 % to 95 % for 105 min in water with a flow rate of 0.2 mL/min. Both solvents contained 0.1 % (v/v) TFA. 100 μ L of each digested sample were injected and monitored at 215 nm.

Example 6: MALDI-TOF spectra of undigested protein

20

An 18 mg/ml solution of trans-3-indoleacrylic acid in acetonitrile/0.1 % trifluoroacetic acid 70/30 (v/v) was premixed with the same volume of sample solution. Then 1.0 μ L of the mixture was applied to the target surface. Typically 150 - 200 laser shots were averaged in linear positive ionisation mode. The accelerating voltage was set to 25.000 V and the grid voltage to 90 %. Bovine albumin M⁺ and M²⁺ were used for external calibration.

Example 7: SE-HPLC (size exclusion HPLC)

30

SE-HPLC was performed with a Waters Alliance 2690 HPLC system equipped with a TosoHaas TSK gel G 4000 SWXL column (7.8 \times 300 mm). Proteins were eluted using a mobile phase containing 0.02 M NaH₂PO₄, 0.15 M NaCl, 1 % (v/v) diethylene glycol and 10 % (v/v) ethanol (pH 6.8) at a flow rate of 0.4 mL/min and detected at 210 nm. The injection amounts were 20 μ g of each isomers.

Size Exclusion HPLC and SDS-PAGE were used to determine the amount of oligo-PEG-IFN alpha 2a forms and aggregates in the different IEC fractions. The reference material contains 2.3 % aggregates and 2.2 % oligomers.

5 Peaks 1, 4, 4a, 5, 6 and 8 contain < 0.7 % of the oligopegylated IFN alpha 2a forms, whereas in peaks 2, 3, and 7 the percentage of the oligopegylated IFN alpha 2a forms are under the detection limit (< 0.2 %). In the case of the aggregates a different trend could be seen. In all peaks the amount of aggregates is below 0.9 %.

Example 8: SDS-PAGE

10

SDS-PAGE was carried out both under non-reducing and under reducing conditions using Tris-Glycine gels of 16 % (1.5 mm, 10 well). Novex Mark 12 molecular weight markers with a mass range from 2.5 to 200 kDa were used for calibration, bovine serum albumin (BSA) was used as sensitivity standard (2 ng). Approximately 1 µg of all the
15 samples and 0.5 µg of standard were applied to the gel. The running conditions were 125 V and 6 W for 120 min. The proteins were fixed and stained using the silver staining kit SilverXpress from Novex.

20 The gels that were recorded under non-reducing conditions for the IEC fractions 1 - 8 show a pattern that is comparable to that of the PEG-IFN alpha 2a reference standard.

Under reducing conditions, the gels show an increase in intensity of the minor bands at about 90 kDa as compared to the standard. Between 6 and 10 kDa protein fragments appear for peaks 6, 7 and 8. Both bands together correspond to approximately 1 % of clipped material. In the lanes of isomer 1, 5, 6, 7, 8 additional bands with more than 100
25 kDa can be seen which are also present in the standard. These can be assigned to oligomers. Thus SDS-PAGE confirms the results of the SE-HPLC analysis.

Overall, RP-HPLC and SDS-PAGE experiments indicate that the purity of the IEC fractions can be considered comparable to the PEG-IFN alpha 2a reference standard.

30 The structure of the PEG-IFN alpha 2a species derived from the 9 IEC-fractions were identified based on the results of the methods described above using the strategy mentioned above.

Example 9: In Vitro Antiviral Protection Activity

The antiviral activities of the isolated isomers were determined by the reduction of the cytopathic effect of vesicular stomatitis virus (VSV) on Madin–Darby bovine kidney (MDBK) cells. The cell lines were cultured in MEM-medium containing 10% fetal bovine serum. The isomers and PEG-IFN were diluted to a final concentration of 10 ng/ml (assay starting concentration) for the detection of the effective concentration. This effective concentration (EC_{50}) was determined as the concentration needed for 50% protection of the cells against the VSV. In all measurements, the cell culture was challenged with VSV 4 hours after addition of the PEG-IFN isomers. After 18 hours growth at 37°C the cells were stained with crystal violet® to determine the number of intact cells.

To determine the antiviral activity of the 9 positional isomers the EC_{50} -values were measured. PEG-IFN was tested in this assay as a reference.

15

Figure 2A shows the specific activities (U/μg, grey columns) of the isomers. In this assay all positional isomers had activity, however at a different level. The isomers K31 with 170% and K134 with 125% display higher values than PEG-IFN. K164 was equal to the mixture whereas the activities of K49, K70, K83, K112, K121 and K131 were lower.

20

Example 10: Antiproliferative Activity Assay.

For this assay, a primary cell culture of human melanoma metastases cells (ME15) was used. This cell line was deposited on August 17, 2000 under the terms of the Budapest Treaty at the Collection Nationale de Cultures de Microorganismes, Institut Pasteur, Paris under the registration number CNCM I-2546. The cell line was cultured in RPMI medium supplemented with 10% FCS, 2 mM glutamine, 1mM sodium pyruvate, 10 mM non-essential amino acids and HEPES buffer (all from Gibco Life Sciences, UK). When confluent, the cells were passaged by trypsinization. Approximately 5000-6000 cells per well in a flat bottom 96 well plate were used as a start point for the cell proliferation assay

30

in the presence or in the absence of the individual concentrations of IFN, PEG-IFN and the isomers over a period of a 5 day period. The number of living cells was then determined using a cell staining kit (Promega, Madison, USA) based on the colorimetric detection of the cleavage of the tetrazolium salt MTS into formazan. The MTS reaction
5 solution was added according to the manufacturer's recommendation for a period of 4 hours at 37°C, after this period the absorption at 490 nm was recorded in a spectrophotometer.

The specific antiproliferative activity of the isomers was determined by using an
10 IFN- sensitive melanoma cell line (ME15) and a commercial assay. Positional isomers and PEG-IFN as references were used at a concentration of 100 U/ml (Figure 2B). The biological unit (U) for the isomers which was used for the experiments was defined and determined in the antiviral assay hereinbefore described, with PEG-IFN as standard reference.

15

In this assay all isomers were active with the isomer K31 at 159% and K134 at 115% relative to PEG-IFN. K164 displayed the same activity as PEG-IFN; all other isomers were less active than the reference.

20 The results rank the activity essentially in the same order as in the antiviral assay indicating that same activities are derived from a common trigger or signalling event.

One explanation for the different specific activities of the nine positional isomers in the two previous experiments could be their different protein stability. To find out this we
25 tested some isomers at different concentrations in a time course experiment using the ME15 cell line. We selected isomers K31 and K134 which have the highest activity, and K121, which is the isomer with the lowest activity, together with IFN and PEG-IFN as references (see Figure 3). Different concentrations of IFN, PEG-IFN and positional isomers (500, 125 and 15 U/ml) were used for the treatment of the ME15 cells over a
30 period of 5 days. Every 24h the number of cells was measured.

Again we found a striking correlation to the antiproliferative activity described above with K134 being most active followed by K31 and PEG-IFN. As expected the lowest activity was found for K121 and IFN.

5 It can be observed that the inhibition of proliferation is decreased by diminishing concentration. Interestingly, PEG-IFN used at a concentration of 500 U/ml exhibits identical antiproliferative activity as compared to the isomer K134 used at 125 U/ml after 5 days, while IFN and K121 exhibit lower or no antiproliferative activity after 5 days when used at a concentration of at least 125 U/ml.

10

In three independent biological assays we established a correlation between the intramolecular attachment site of the PEG moiety and the biological activity. In summary, the isomers K31 and K134 showed consistently higher specific activities than the commercial mixture, while the remaining seven isomers had a similar specific activity
15 compared to the commercial mixture (K164). Activities range between 170% and 20% indicating that the difference in specific activities of the protein between the positional isomers is significant.

Example 11: Expression and purification of the recombinant extracellular domain of the
20 Interferon Receptor 2 from *E.coli*:

The extracellular domain of the Interferon Receptor 2 (IFNR2-EC) was cloned into a pET15b-vector (Invitrogen, US) with an N-terminal His-Tag[®]. This vector construct was used to express IFNR2-EC in *E.coli*. The target protein precipitated in the cells in the form
25 of inclusion bodies. The *E.coli* pellet after the fermentation in full medium was resuspended in lysis buffer containing 50 mM Tris, 10% saccharose, 0.02% sodium azide, 10 mM magnesium chloride and EDTA-free protease inhibitor. After the homogenisation in a French Press and centrifugation (13000 rpm) the inclusion bodies were solubilized in 8 M urea. The first chromatography step was a nickel chelate chromatography with a linear
30 gradient from 0-500 mM imidazol over 10 column volumes. The pooled peak of IFNR2 was dialysed against 8 M urea to remove the imidazol. After this dialysis the sample was

diluted to 0.1 A₂₈₀ with 8 M urea containing 150 mM Tris/HCL pH 8.0 and stored at room temperature until the Ellman assays were negative. The oxidised IFNR2-EC was dialysed against 50 mM Tris pH 8.4 for refolding. 50 mM Tris pH 8.4 was also the starting buffer for the second chromatography. The second chromatography step was with an anion ion-exchange resin (HiTrap Q HP, 5x5ml, Amersham Biosciences) with a gradient of 0-500 mM NaCl.

All purification steps were analysed by SDS-PAGE under reduced and non-reduced conditions. The protein purity was monitored by analytical size-exclusion chromatography using Superdex[®] 75 and 200 HR (PC 3.2/30, Amersham Biosciences). This chromatography method was also used to determine both the binding activity and capacity (data not shown).

Example 12: Characterisation of the interaction of IFN and the PEG-IFN isomers with the IFNR2-EC using an optical biosensor system:

The immobilisation of the IFNR2-EC was achieved by labelling with biotin. The biotinylated protein was anchored to a streptavidin sensor surface (SA Sensor, BIAcore).

Biotinylation was performed by diluting the protein stock solution (10 mM acetate, pH 7.5) with Hepes (10 mM, pH = 8.4) to a final protein concentration of 0.23 mg/ml protein (8.65 μ M). A 8.65 mM solution of biotinamidocaproate-n-hydroxysuccinimide ester (Fluka) in DMSO was added to the solution to give a final concentration of the biotinylating reagent of 86.5 μ M. The mixture was allowed to react for 1h before it was dialysed over night against a Hepes buffer (10 mM, pH 8.4, 150 mM NaCl) to remove low molecular weight reaction products. This solution was used in the immobilisation procedure. Immobilisation was achieved by contacting the solution of the biotinylated protein with the SA sensor surface. The amount of immobilised protein was controlled via the contact time. For the binding experiments 4000 RU, corresponding to approximately 4 ng/mm² of protein were immobilised.

Binding experiments were performed in Hepes buffer (10 mM Hepes, 150 mM NaCl, 3 mM EDTA, 0.005% polysorbate 20, pH 7.4) as the running buffer. Interferon solution was prepared by diluting stock solutions of the proteins with running buffer. The flow velocity was set to 5 μ l/min for all binding experiments. The interferon solutions were
5 contacted for a time interval of 5 min with the immobilised IFNR2-EC.

Calculation of binding data: dissociation constant (K_D) values were determined by fitting the time dependent response curves with a mathematical fit based on the simple kinetic model of the formation of a 1/1 complex. k_{on} and k_{off} values were obtained from this
10 fit. K_D represents the ratio k_{off}/k_{on}

Investigation of the interaction of proteins by label-free solid phase detection such as surface plasmon resonance (SPR) requires the immobilisation of one of the interacting compounds.
15

We used two different coupling strategies to immobilise IFN or IFNR2-EC to the sensor surface. The IFN was immobilized via free amino groups on a carboxylated dextran sensor surface, the IFNR2-EC was labeled with biotin and anchored to a streptavidin sensor surface. With these two sensors and the corresponding IFN respectively IFNR2-EC
20 binding test were done. Consistent values of rate constants and binding affinities were obtained. The results indicate that the binding affinity is independent of the immobilization technique and the immobilized protein (data not shown). These preliminary tests were necessary to increase the accuracy for the measurements with the isomers and to verify the simple kinetic model of 1/1 complex formation.

25

For the determination of the affinity and kinetic constants we selected five isomers (K31, K121, K131, K134 and K164) to cover the whole activity range of the specific biological activity (see Figure 2 A,B). To increase the significance of the kinetic and equilibrium parameters, we performed binding studies on the immobilized IFNR2-EC
30 with different concentrations of the isomers. The IFN and PEG-IFN were used as a reference. The result of the binding curve fits based on a kinetic model for a formation of a 1/1 complex are given in Table 2.

	k_{on}	k_{off}	K_{Dkin}
	$[10^5 \text{ M}^{-1}\text{s}^{-1}]$	$[10^{-2} \text{ s}^{-1}]$	$[\text{nM}]$
IFN	12.5	1.14	9.12
PEG-IFN	0.27	2.3	851
K_{31}	n.d.	n.d.	n.d. ($> 1\text{mM}$)
K_{134}	0.87	3.96	455
K_{131}	0.96	2.8	289
K_{121}	0.83	2.33	279
K_{164}	2.19	0.652	335

Table 2: Kinetic constants for the interaction of wild-type IFN; PEG-IFN and several positional isomers

5 The table shows the measured affinity and kinetic data. The calculation for the kinetic constant is based on the kinetic model of a 1/1 complex formation. The IFNR2-EC was labelled with biotin. This biotinylated protein was anchored to a streptavidin sensor surface (SA Sensor, Biacor). Binding experiments were performed in Hepes buffer (10 mM Hepes, 150 mM NaCl, 3 mM EDTA, 0.005% polysorbate 20, pH 7.4) as the running buffer.

10

The obtained K_D -values indicate that the pegylation of IFN causes a decrease in the affinity towards the INFR2-EC. The affinity deficit is dependent on the position of pegylation. The affinity change is generally due to a change in the association constants (k_{on}). For instance, isomer K134 changes the affinity roughly by a factor of 15. k_{on} is reduced by a factor of more than 10, whereas k_{off} is increased only by a factor of approximately 4.

15

For the isomer K31 only an estimation of the K_D was possible because the protein concentrations were too low.

Combining the data from the specific antiviral or specific antiproliferative activity with the IFNR2-EC affinity study an interesting correlation was observed as seen in Figure 4. It indicates that the higher the IFNR2-EC affinity (low K_D) of a given isomer, the lower the specific biological activity. This correlation is opposed to the common drug screening dogma which is principally used to search ligands which have a low K_D and a high biological activity.

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Example 13: Transcriptional response of the isomers compared to IFN

DNA microarrays which permit simultaneous measurement of the expression levels of thousands of genes, provide a comprehensive frame-work to determine how the positional isomers affect cellular metabolism and regulation on a genomic scale.

15

To estimate the influence of the pegylation site on the transcriptional activity of IFN we measured the IFN-induced gene expression pattern of the melanoma cell line ME15 via the oligonucleotide array technology

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ME15 cells were incubated for 48h with 100 U/ml of IFN, PEG-IFN or PEG-IFN isoforms. After 48h the cultured cells were harvested by scraping and the total cellular RNA was extracted with RNA-BeeTM. From each sample 10 µg of the total cellular RNA were reverse transcribed (Invitrogen, U.S.), labelled (Ambion, U.S.) and processed by using commercial kits according to the supplier's instructions. The methods of the alkaline heat fragmentation and the following hybridisation of the cDNA with the U95Av2 GeneChip arrays were standard procedure provided by the manufacturer of the microchips (Affymetrix, U.S.). A further example for a procedure for performing oligonucleotide array analysis can be found in Fambrough et al., Diverse signaling

25

pathways activated by growth factor receptors induce broadly overlapping, rather than independent, sets of genes, *Cell* 97 (1999), 727-741.

5 The raw data of the arrays were measured with a confocal laser scanner (Hewlett Packard, U.S.) and pixel levels were analysed using GeneChip v3.1 software (Affymetrix, U.S.). The expression level for each gene was calculated as normalised average difference of fluorescence intensity as compared to hybridisation to mismatched oligonucleotides, expressed in arbitrary units (AD). Each investigation of the samples was measured in triplicate with labelled cRNA from three different cell plates.

10

The following four criteria were chosen for differential expression of a gene after treatments with IFN, PEG-IFN or the PEG-IFN isoforms compared to the untreated cells were: (1) The intensity value of the treated cells is at least two fold higher than the untreated cells. (2) The intensity value in the treated cells should be higher or at least 50 AD. (3) The intensity value of the untreated cells should be lower than 50 AD. (4) The standard deviation has to be significantly smaller than the absolute change in average difference and the calculated confidence level of a gene is set greater than 97% (p value < 0.03).

20 For these experiments we used the same cell line (ME 15) as for the antiproliferative assay. We treated the cells for 48h with 100 U/ml of each isomer or with IFN and PEG-IFN. IFN was used as the reference. After this treatment total RNA was isolated from the ME-15 cells. The methods for preparation of cRNA and subsequent steps leading to hybridization and scanning of the U95Av2 GeneChip Array are described above. Visual inspection of total RNA samples before processing by agarose gel electrophoresis did not reveal any signs of degradation or yield in the samples. The number of biological replicates for each isomer, IFN and PEG-IFN (n=3) allows the application of statistical algorithms for data analysis in order to account for experimental variation. The data analysis focused on genes which were lower than 50 AD in the untreated cells but at least 2-fold upregulated with an AD value of at least 50 in the treated cells.

25

30

The standard deviation had to be significantly smaller than the absolute change in average difference and the calculated confidence level of a gene was set to greater than 97% (p value < 0.03).

5 By applying these criteria, an expression profile of 29 upregulated genes was observed. In this expression pattern 13 known IFN-inducible genes which are involved in the antiproliferative and antiviral pathway were highly upregulated as compared to IFN (Table 3). The hierarchical cluster (Figure 5B) illustrates that all isomers have transcriptional activity but generate different intensities.

10

The sum of AD (Σ AD) of the induced genes was determined for each isoform and IFN, and the transcriptional, antiviral and proliferative activities compared with IFN as a reference. Figure 5 A shows that isoforms with an increased biological activity, as determined by their antiviral and antiproliferative activities as compared to PEG-IFN, also
15 have an increased transcriptional activity, while isoforms with a lower biological activity display a lower transcriptional activity, and that thus, in contrast to biological activity vs. binding assays, a positive correlation exists between biological and transcriptional activity.

Beside the effect of the isomers on the general transcriptional gene response, a varied
20 upregulation of individual genes was also observed. For example, the gene for interferon-induced nuclear phosphoprotein shows higher expression upon exposure to K49 and K31 than with K134 or K131. K49 and K31 isomers have a lower general transcriptional gene response than K134 or K131. This observation emphasizes the necessity of analysing the general transcriptional gene response, as determined by the method of this invention,
25 rather than to measure transcriptional expression levels of an individual gene, or a small selection of genes, for the determination of the transcriptional activity of a compound of interest.

The data of the microarray chips were also analyzed for transcriptional-specific side-
30 effects which may indicate undesirable effects on the metabolism or vitality of cells by any isomer. The criteria for these analyses were similar to those described before, the only

difference was that the data for each isomer were cross-compared. The result of this analysis showed no specific side-effect of any positional isomer.

Gene discription	Seq ID No.	Untreated Intensity	IFN	PEG-IFN	K134	K70	K112	K49	K131	K31	K83	K164	K121
Interferon-alpha induced 11.5 kDa protein (p27). Bone marrow stromal antigen 2 (BST-2). Interferon-induced protein 6-16 precursor (Ii-6-16). Interferon-induced17/15-kDa protein mRNA expressed in osteoblast ISGF-3 components (p91/p84) ISGF-3 gamma (p48) Hepatitis C-associated p44 Interferon-induced 56 kDa protein (IFIT-1) Interferon-inducible protein 9-27 2'-5'-oligoadenylate synthetase 1 (1.6Kb) Wilms' tumor associated protein (WIT-1). Interferon regulatory factor 7 (IRF-7). Interferon-induced 60 kDa protein Nuclear autoantigen Sp-100 KIAA0793 protein 2'-5'-oligoadenylate synthetase 2 (71 kDa) Histone H2A.g (H2A/g)	1	4	609	921	876	705	639	514	481	344	444	284	202
	2	11	554	714	681	701	507	544	542	463	476	390	362
	3	42	783	863	890	795	875	594	499	607	580	547	437
	4	27	367	503	750	681	492	469	461	352	396	305	187
	5	8	132	201	240	226	128	114	139	133	80	91	60
	6	36	230	291	325	303	302	296	208	229	286	171	165
	7	45	213	175	179	196	255	210	145	155	227	109	126
	8	11	93	111	126	102	93	65	89	69	69	57	54
	9	9	93	120	171	162	70	75	100	84	77	65	39
	10	8	74	134	220	200	112	89	66	69	53	49	25
	11	2	67	95	164	148	73	78	68	97	60	62	46
	12	6	57	38	66	21	52	75	41	33	25	51	17
	13	10	52	72	102	83	54	68	61	84	56	72	51
	14	13	48	58	68	85	37	51	56	46	38	46	30
	15	31	72	66	96	73	44	52	55	53	45	56	51
	16	44	99	71	66	59	162	119	63	101	133	85	61
	17	32	71	112	144	150	68	61	71	53	48	52	52
	18	14	39	28	58	27	93	82	25	59	74	59	28

Interferon-induced nuclear phosphoprotein	29	14	37	44	88	76	48	38	45	53	35	40	41
Probable G protein-coupled receptor GPR12	19	31	52	79	50	60	82	92	75	121	25	83	37
Cytochrome P450 XXIB (Steroid 21-hydroxylase)	20	34	56	60	102	48	63	50	75	68	45	53	51
putative tumor suppressor protein (101F6)	21	24	35	31	47	42	62	76	45	53	58	51	51
Transcription factor E2-alpha (TCF-3)	22	23	32	32	50	52	26	35	74	31	31	55	22
KIAA0691 protein	23	41	56	59	110	106	82	90	114	93	81	125	79
5-hydroxytryptamine 1B receptor (Serotonin)	24	19	26	21	64	24	26	25	26	32	27	34	23
Coagulation factor XII precursor (Hageman factor)	25	22	27	45	35	41	66	47	16	31	51	44	37
Proto-oncogene tyrosine-protein kinase ABL1 (p150)	26	21	26	31	50	27	16	30	69	43	38	23	31
Protein AF1q	27	13	16	34	47	65	50	61	43	49	40	46	46
Guanidinoacetate N-methyltransferase (GAMT)	28	21	15	16	15	43	71	50	36	18	41	54	23

Table 3: IFN modulated genes dependent on the pegylation side

Table 3: IFN modulated genes dependent on the pegylation side

To identify induced genes the ME15 cell line were cultured 48 hours in absence (untreated cell) or in presence of 100 U/ml IFN or a PEG-IFN sample. The expression level for each gene was calculated as normalised average difference of fluorescence intensity as compared to hybridisation to mismatched oligonucleotide, expressed in arbitrary units. Each investigation of the samples were measured in triplicate with labelled cRNA from three different cell plates. The criteria for a differentially expression of a gene by treatments with IFN or a PEG-IFN sample compared to the untreated cells were: if the mean value increase was at least twofold higher as in the untreated cells and the main value in the treated cells should be higher or at least 50 units. The mean value of the untreated cells should be lower than 50 units. In addition, the standard deviation had to be significantly smaller than the absolute change in average difference and the calculated confidence level of a gene was set greater than 97% (p value < 0.03). By applying these criteria, 29 genes were found to be modulated.

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Claims

1. A method for determining the biological activity of a compound which can modulate gene transcription, comprising the steps of
 - a) contacting a host with a compound;
 - 5 b) determining the general transcriptional gene response of the host; and
 - c) quantitating the general transcriptional gene response induced by said compound.
2. The method of claim 1, wherein the general transcriptional gene response is determined by a DNA array technology.
- 10 3. The method of claim 2, wherein the DNA array technology is an oligonucleotide array technology.
4. The method of any one of claims 1 to 3, wherein the compound is a modified
15 compound.
5. The method of claim 4, wherein the modified compound is a modified protein.
6. The method of claim 5, wherein the modified protein is a pegylated protein.
- 20 7. The method of claim 6, wherein the pegylated protein is a specific isolated isoform of a pegylated protein.
8. The method of claims 6 or 7, wherein the pegylated protein is Epo or INF.

9. The method of any one of claims 1 to 8 wherein the transcriptionally regulated genes are one or more genes selected from the group consisting of Seq ID No. 1 to 29.
- 5 10. A method for determining the relative biological activity of a modified compound, comprising measuring the biological activity of the modified compound and the respective unmodified compound by the method of any one of claims 1 to 7, wherein the relative transcriptional activity of the modified protein is determined by calculating the ratio of the biological activity of the modified compound and the biological activity
10 of the unmodified compound.
11. The method of claim 8, wherein the modified compound is a chemically or enzymatically modified compound.
- 15 12. The method of claim 9, wherein the modified compound is a pegylated protein.
13. A method for identifying compounds that indirectly modulate gene transcription comprising determining the biological activity of a first compound which is a known modulator of gene transcription by the method of any one of claims 1 to 9 in the
20 presence or absence of a second compound, wherein a compound which indirectly modulates gene transcription is identified if the biological activity of the first compound measured in the presence of said second compound is significantly different from the biological activity of the first compound measured in the absence of said second compound.
- 25 14. The method of claim 13 wherein the known modulator of gene transcription is Epo or IFN.

15. A compound identified by the methods of claims 1 to 14 which modulates gene transcription.
16. Use of the method of claims 1 to 14 for identifying a compound which modulates gene transcription.
17. A kit comprising components for carrying out the methods according to claims 1 to 14.
18. The kit of claim 17 wherein said components comprise a DNA array.
19. A pharmaceutical composition comprising a compound of claim 15 and a pharmaceutically acceptable carrier.
20. Use of a compound of claim 15 or a pharmaceutically acceptable salt thereof for the preparation of a medicament for the treatment of a disease, preferably a viral disease or of a cancer.
21. The methods, compounds, kit and uses as hereinbefore described, especially with reference to the foregoing examples.

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21 März 2003

Abstract

The present invention provides a novel method for determining the biological activity of a compound comprising the steps of a) contacting a host with a compound; b) determining the general transcriptional gene response of the host; and c) quantitating the general transcriptional gene response induced by said compound.

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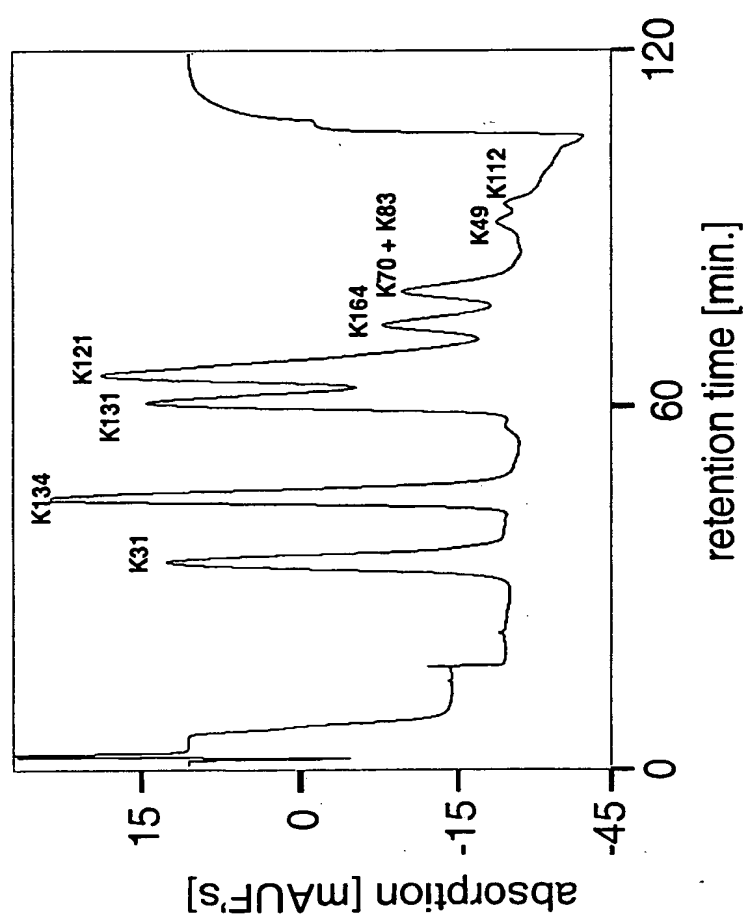


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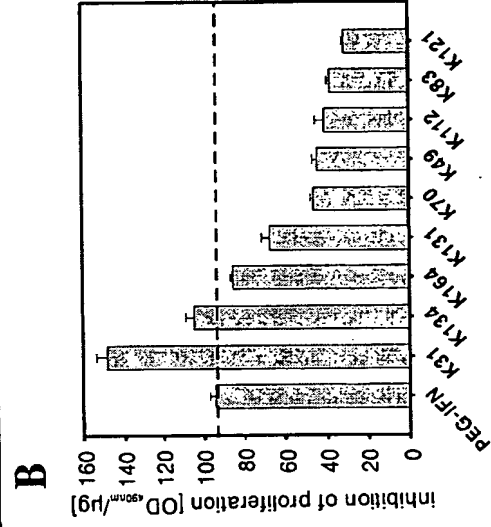
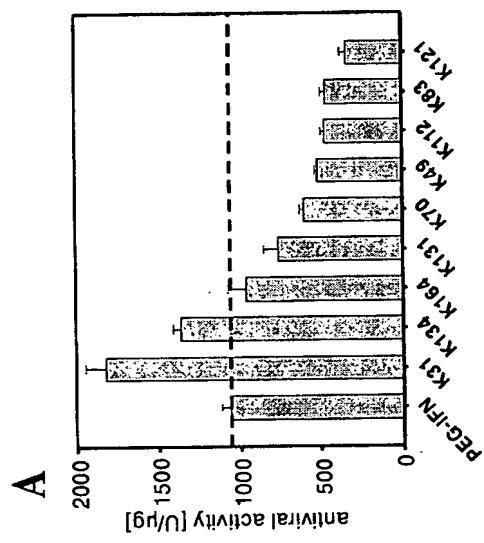


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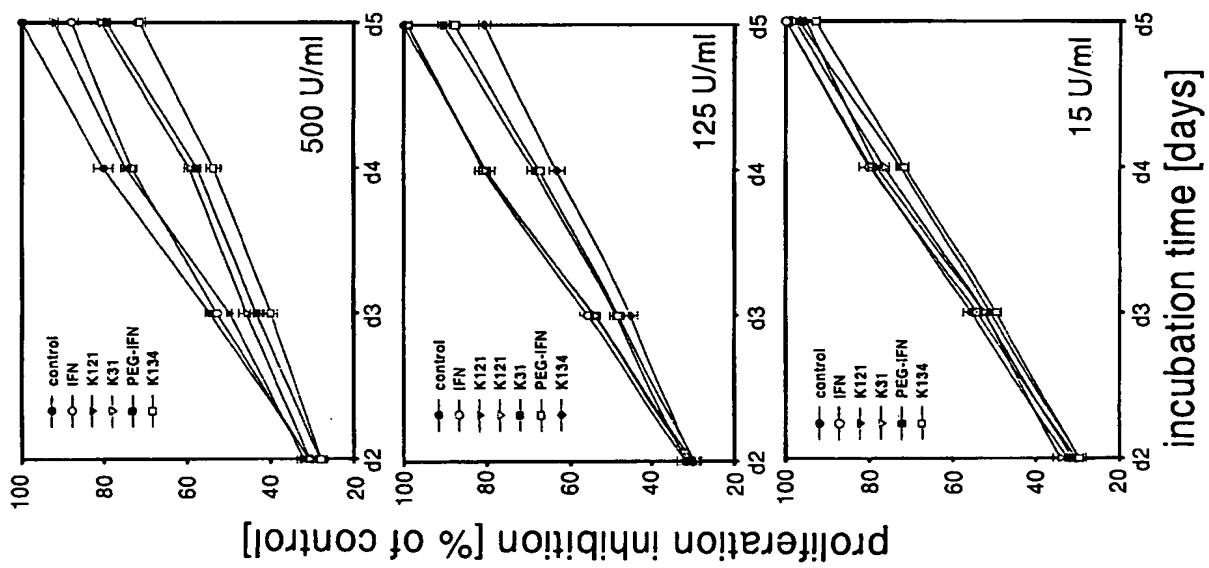
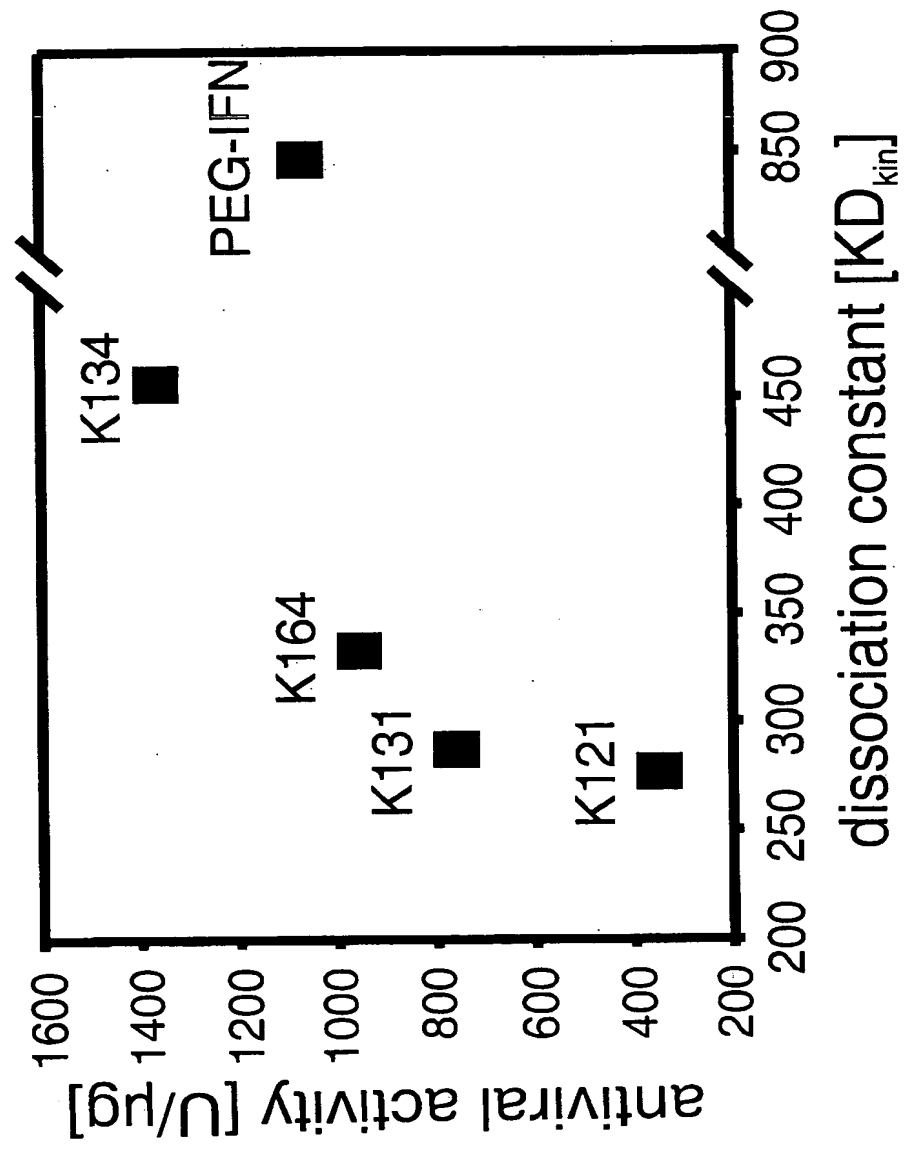


Figure 3

Figure 4



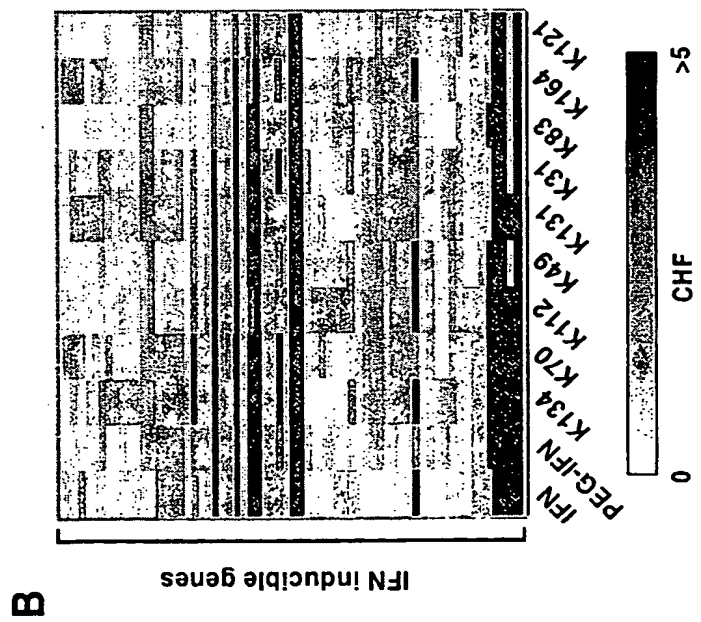
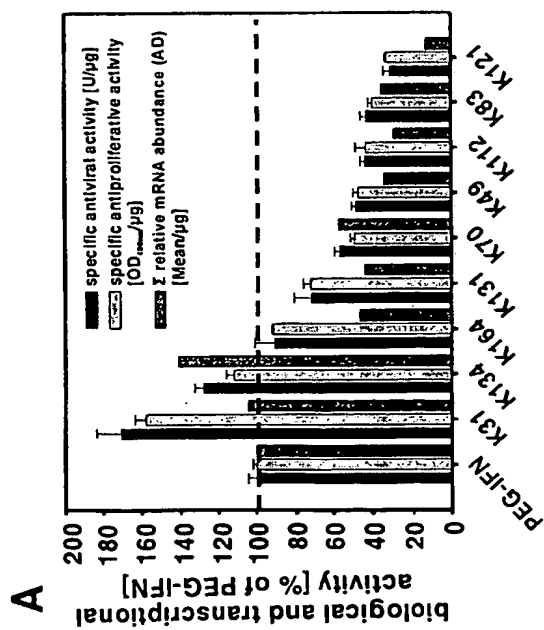


Figure 5

The diagram illustrates the classification of Kunitz-type protease inhibitors into four groups based on their specific biological activity. The inhibitors are represented by ribbon models, and arrows indicate their assignment to one of the four groups.

- group 1:** Includes K₃₁, K₁₃₄, and K₁₃₁.
- group 2:** Includes K₁₆₄, K₁₂₁, K₈₃, and K₇₀.
- group 3:** Includes K₄₉ and K₇₀.
- group 4:** Includes K₈₃, K₁₁₂, and K₁₂₁.

Each group shows the inhibitor's structure in its front view and a view rotated 90°.

Specific Biological Activity

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<223> GenBank accession No. M87503

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15 <213> Homo sapiens

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<222> (1)..(483)

<223> GenBank accession No. D28915

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<223> X04371

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<223> GenBank accession No. AF040704

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